Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Defining long COVID: Going back to the start

Nisreen A. Alwan[1,2,3,*] and Luke Johnson[1]

"Long COVID" is the condition whereby affected individuals do not recover for several weeks or months following the onset of symptoms suggestive of COVID-19, whether tested or not.[1] The name "long COVID" was created by the people experiencing it in Spring 2020 to describe their journeys of not recovering.[2] Here, we suggest a way to standardize its definition through outlining what constitutes initial infection with COVID-19.

In previously hospitalized COVID-19 patients, persistent ill health seems to be very common, with ongoing symptoms including breathlessness, cough, fatigue, and mental health problems.[3] However, long COVID is not restricted to those with initial severe disease. In many so-called "mild" COVID-19 cases, recurring symptoms include persistent fatigue and breathlessness, headache, chest heaviness, muscle aches, and palpitations. They involve many systems and are wide-ranging, with a mostly fluctuating or relapsing nature. A large proportion of those who do not fully recover also develop cognitive problems, including poor memory and concentration, as well as what "long haulers" describe as "brain fog."[4] There is emerging evidence of long-term health impairment and organ damage across the spectrum of the clinical presentation of COVID-19 infection.[5] However, much is still unknown about long COVID. Most importantly, it is still not well defined for the purposes of clinical diagnosis, disease surveillance, and research.

How common is long COVID?

Measuring COVID-19 morbidity is an immediate priority in this pandemic. There are two main issues to be taken in account when measuring the prevalence of long COVID, particularly in non-hospitalized individuals with non-laboratory confirmed infections. First, everyone infected with COVID-19, or at least all those initially symptomatic, should be counted in the denominator. Second, standardization of case definitions, especially for the comparison across different settings and population groups, needs to be applied.

Evidence from relatively small studies suggests approximately one-third of

[1]School of Primary Care, Population Sciences and Medical Education, Faculty of Medicine, University of Southampton, Southampton, UK

[2]NIHR Southampton Biomedical Research Centre, University of Southampton and University Hospital Southampton NHS Foundation Trust, Southampton, UK

[3]NIHR Applied Research Collaboration Wessex, Southampton, UK

*Correspondence: N.A.Alwan@soton.ac.uk

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non-hospitalized COVID-19 patients do not fully recover and have symptoms after 2–6 weeks from the onset of disease or a positive PCR test.[6,7] Around 11%–24% of COVID-19 cases have been reported to still have persisting symptoms 3 months after onset of illness.[8,9] One study reported persistence of at least one symptom after a mean of 125 days from onset in 53% of those included.[10]

Estimates from the UK's Office of National Statistics (ONS), derived using a Kaplan-Meier approach based on a sample of 8,193 respondents, point to a long COVID prevalence of 21% at 5 weeks and 10% at 12 weeks from onset.[11] However, this was based on a list of 12 symptoms as asked by the ONS COVID-19 infection survey, with some of the common symptoms of long COVID such as chest heaviness, palpitations and neurological manifestations not included.

Estimates vary because of different study designs, recruitment settings, questionnaires, symptoms, and recovery assessment. One way to measure the prevalence of long COVID is by negative definition: it is a lack of full recovery from COVID-19 infection. However, current surveillance systems do not assess recovery in any standardized or consistent way. This could be done by test and trace national and local infrastructures following up those who test positive for COVID-19 at 4, 8, and 12 weeks and asking them quick questions about whether they are back to their baseline health before infection.

Long COVID case definitions

Standard clinical case definitions would provide healthcare professionals with systematic and inclusive criteria to diagnose patients with ongoing symptoms. However, these definitions must not be entirely dependent on laboratory diagnosis. Many people who were not hospitalized in the first wave of the pandemic did not have access to testing. Long haulers often face the complication of lack of formal clinical diagnosis of their acute COVID-19 illness because of issues with lab test availability, accessibility, feasibility, and accuracy in the early phase of the pandemic. In addition, many of these patients would not have initially required or sought medical care and this can potentially result in later health concerns not being adequately addressed.

In addition to the lack of accurate tests in the early phases, social and demographic disparities also risk exacerbating health inequalities. There are still numerous disincentives to seeking testing early in the illness. These include stigma, difficulty in accessing tests, and barriers against self- and household isolation including loss of income, care networks, and essential social support. These disincentives are much stronger in disadvantaged populations. Lack of lab confirmation means many people experiencing long COVID encounter barriers against healthcare, sick pay, and benefits access.

The recent National Institute for Health and Care Excellence (NICE) rapid guideline on managing the long-term effects of COVID-19 stresses the importance of not excluding people from clinical assessment in the absence of a positive SARS-CoV-2 test. It uses the terminology of "ongoing symptomatic COVID-19" for "signs and symptoms of COVID-19 from 4 to 12 weeks" and "post-COVID-19 syndrome" for "signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks, and are not explained by an alternative diagnosis" (https://www.nice.org.uk/guidance/ng188). These definitions are very broad and do not outline the initial or subsequent patterns of symptoms as criteria to help lessen the variation in diagnosis and referral among different clinicians.

A contributing factor to the lack of clinical diagnosis is that there is still no formal guidance on criteria to determine probable initial COVID-19 infection for those presenting with long COVID symptoms. One way to standardize and facilitate diagnosis and make it more inclusive is to use a retrospective case definition. Until we know more about the clinical presentation of long COVID, establishing the initial acute episode using set criteria can provide a route to the diagnosis of long COVID. This can be used not only clinically, but also to inform surveillance estimates of COVID-19 persistent symptoms and pathology. We need to use acute COVID-19 case definitions to inform a definition of the initial infection in those presenting later with persistent symptoms.

Acute COVID-19 case definitions

Currently, case definitions and diagnostic criteria for "possible," "suspected," and "probable" acute COVID-19 vary between countries and international public health agencies. Clinical criteria alone define a possible/suspected case in most national/international case definitions. WHO also considers "new onset anosmia or ageusia in the absence of any other identified cause" as sufficient for probable COVID-19 (https://www.who.int/publications-detail-redirect/WHO-2019-nCoV-Surveillance_Case_Definition-2020.1). Criteria for a confirmed case are invariably lab based, mostly by nucleic acid amplification tests (NAAT), most commonly polymerase chain reaction (PCR).

Epidemiological criteria are understandably heterogenous due to variation in local prevalence of COVID-19. Some country case definitions focus on whether an individual has recently traveled internationally or has been in contact with a probable or confirmed case. Others include places or gatherings known to be outbreaks. Some, including WHO's, pragmatically include communities or regions of known high transmission as a

sufficient risk factor in their epidemiological criteria. Several countries already have case definition criteria which would potentially enable retrospective diagnosis, whether by clinical and epidemiological history, or through an antibody test.

Past acute COVID

Here, we propose criteria for retrospective diagnosis of COVID-19, which we refer to as "past acute COVID." These can be used to define initial COVID-19 infection in those with persistent illness, particularly those who do not have laboratory confirmation of the acute infection and did not obtain a clinical diagnosis of it in the first two weeks from the onset of the symptoms. We propose any one of the following criteria would be sufficient for diagnosis for Long COVID:

1) Positive SARS-CoV-2 PCR or antigen test during the acute phase.
2) Positive SARS-CoV-2 antibody test at any time point in the absence of SARS-CoV-2 vaccination history.
3) Loss of sense of smell or taste during the acute phase in the absence of any other identified cause.
4) Symptoms consistent with SARS-CoV-2 infection during the acute phase AND high prevalence of COVID-19 at time and location of onset.
5) At least one symptom consistent with SARS-CoV-2 infection during the acute phase AND close contact of a confirmed case of COVID-19 around the time of onset.

However, these criteria present some caveats. They do not account for those who did not have lab confirmation and were completely asymptomatic during the acute phase. COVID-19 antibody tests have variable sensitivity but high specificity, and antibody titers are likely to reduce the longer after infection an individual is tested.[12,13] Therefore, a positive result would be sufficient to diagnose past acute COVID, but a negative result insufficient to exclude it.

Loss of sense of smell and taste has been shown to be the symptom which best predicts acute COVID-19 and has been used as a definition by the WHO for a probable case.[14] We therefore argue it is sufficient to be used alone here for diagnosing past acute COVID-19 too.

For the clinical symptoms definition in criteria 4 and 5, at the present we propose the WHO clinical criteria of either the presence of both acute onset fever and cough or the combination of any three or more of the following symptoms and signs: fever, cough, general weakness/fatigue, headache, myalgia, sore throat, coryza, dyspnoea, anorexia/nausea/vomiting, diarrhea, and altered mental status.

Finally, the criterion of "high prevalence of COVID-19" must be country and time specific. Prevalence can be underestimated depending on the availability of testing within a country during a given time period. One source of regional prevalence information could be regular random national COVID-19 prevalence surveys.

Standardizing retrospective case definitions for COVID-19 has two primary purposes. First, it will enable clinicians to retrospectively diagnose COVID-19, enabling them to order relevant investigations and provide patients with long COVID access to treatment and rehabilitation. By providing a solid diagnosis, clinicians will be able to treat long haulers even if they present with an unusual spectrum of symptoms. Second, it will enable surveillance systems to better assess the prevalence of COVID-19 morbidity, thereby informing the planning of public health services and interventions.

The proposed criteria could be a starting point for a more structured expert working group consensus approach, particularly around refining the clinical symptom and prevalence criteria. Once the natural history and clinical spectrum of long COVID symptoms are well established, additional criteria relating to the presence of typical long COVID symptoms could be added to be used alongside the retrospective case definition. Until then, we believe the five criteria presented above provide a guide for the diagnosis of past acute COVID, which then forms the basis of counting and managing long COVID, including cases that have not been initially lab confirmed.

It is also worth noting that case definitions have multiple purposes including surveillance, clinical diagnosis, and research. It is desirable for the purposes of clinical diagnosis that the criteria are as sensitive, equitable, and inclusive as possible to avoid disadvantaging certain population groups and excluding them from access to services, support, and welfare benefits.

Long COVID open questions

Past acute COVID criteria start to address one of the main pressing questions around long COVID diagnosis and definition. In addition to ascertaining the prevalence of long COVID in different population groups, which is an immediate priority (counting long COVID), there are many other open questions in this area. We still do not know who is more likely to get long COVID and what the risk factors for developing it are. We also do not know who is more likely to recover from it, and how it can be treated. To answer these questions, we need to understand the underlying pathophysiological mechanisms; for example, whether there is genetic susceptibility to long COVID, and whether immune, inflammatory, or persistent infection mechanisms are implicated. Long

COVID is currently an umbrella term that may be more than one medical condition.

We need to characterize the distinct patterns of symptoms, and understand whether they can predict progression, prognosis, and response to treatment. One important research avenue is to investigate what can be done in the acute phase of COVID-19 infection to prevent progression to long COVID. We still do not know whether long haulers are more or less likely to get re-infected, particularly if the pathophysiology involves inadequate immune response, and whether this means clinical deterioration. Follow-up of vaccinated people with long COVID is essential to understand the effect of the vaccine on disease progression.

We need to quantify the burden long COVID exerts on the economy, health, and care systems. Widening health inequalities is a likely outcome of COVID-19 morbidity, therefore we must discuss how disadvantaged and marginalized groups affected by long COVID will be protected in term of care, prevention, and employment rights.

COVID-19 infection can no longer been described in black and white. There is a huge gray area of those who survived COVID-19 in the short-term but have not recovered. One of the main challenges of the next phase of this global pandemic is to quantify long COVID, prepare the different systems across society for its enormity, help those affected by it in an equitable manner, and prevent more from progressing to it. This is the task ahead of us. It is extremely complex and daunting but unavoidable.

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AUTHOR CONTRIBUTIONS

N.A.A. conceived the article's concept. Both authors drafted and finalized the manuscript.

DECLARATION OF INTEREST

The authors declare no financial conflicts of interest. N.A.A. had/has symptoms of long COVID. In October 2020, N.A.A. provided expert feedback in relation to one scoping meeting for the NICE/SIGN/RCGP Long COVID Rapid Guideline.

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